REMARKS

Claims 30, 71, 76, 85-88, 96, 99, 100, 103-114, 117-119, and 123-134 constitute the pending claims in the instant application. New Claims 129-134 are added to further clarify the subject matter claimed. Support can be found throughout the specification, *see*, for example, page 44, 2nd full paragraph; page 16, 1st full paragraph; and page 45, 2nd full paragraph. No new matter is introduced. Claim 98 has been canceled.

Applicants note that in the pending non-Final Office Action, the Examiner has advanced a new ground of enablement rejection never before advanced during the eight-plus-year prosecution of the instant application despite prior presentation of claims of similar or broader scope. Pursuant to MPEP 707.07(g), "[p]iecemeal examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references. *See* MPEP § 904.03. Major technical rejections on grounds such as lack of proper disclosure, lack of enablement, serious indefiniteness and *res judicata* should be applied where appropriate even though there may be a seemingly sufficient rejection on the basis of prior art." Thus, Applicants would appreciate the Examiner's confirmation that the pending claims have been fully and completely examined at this time.

Applicants have amended the specification to provide complete evidence of the deposit of the antibodies referred to in Claims 88, 123-128, and 133, by specifically reciting the date of deposit and the complete name and address of the depository. Applicants state that the mouse hybridoma B43.13 (MCB-ALT-96), which produces the antibody B43.13, was deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209, on May 18, 2000, and was given ATCC deposit number PTA-1883.

Applicants' attorney hereby states that the deposit has been accepted by an International Depository authority - the American Type Culture Collection (ATCC) - under the provisions of the Budapest Treaty, and that upon the grant of a patent on this application with claims referencing the deposited hybridoma, all restrictions upon public access to the deposit will be

irrevocably removed, and that the deposit will be maintained for the required time and replaced if viable samples cannot be dispensed by the depository if required.

Attached as **Exhibit B** is a copy of the deposit receipt from the American Type Culture Collection (ATCC).

Furthermore, Applicants have amended the specification to recite the date of deposit and the complete name and address of the depository.

Because the deposit was made after the effective filing date of the application, Applicants hereby submit a copy of a verified statement from inventor Birgit C. Schultes, Ph.D., to satisfy the requirement under 37 C.F.R. § 1.804(b).

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claims 30, 71, 76, 85-87, 96, 98-100, 103-114, 117-119 are rejected under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for a method of treating an oncological disease comprising administering to a host a complex formed from CA 125 and a monoclonal antibody or antigen-binding fragment thereof that binds to CA 125, and wherein the complex induces host antibodies and cytotoxic T-cells reactive with at least one other epitope of the tumor associated antigen," allegedly "does not reasonably provide enablement for the administration of any other complex of a soluble tumor antigen and a monoclonal antibody or antigen-binding fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims."

Applicants first note that the Examiner has previously (*see* page 2, last paragraph of the November 2, 2005 Office Action), and again in the current Office Action (*see* page 2, third paragraph of the current Office Action) acknowledged the enablement of claims directed to "a method of treating an oncological disease comprising administering to a host a complex formed from CA 125 and a monoclonal antibody or antigen-binding fragment thereof that binds to

CA 125, and wherein the complex induces host antibodies and CTL reactive with at least one other epitope of the tumor-associated antigen." The rejection here appears to be directed to the enablement of administering *any other complex* of a soluble tumor antigen and a monoclonal antibody or antigen-binding fragment thereof. However, the pending claims recite a complex of the soluble tumor antigen CA 125, not *any other complex*. Thus the reasoning of the Office Action as discussed below appears to be inconsistent with the stated rejection and the Examiner's admissions. Nonetheless, Applicants have responded to the Examiner's comments below.

The Examiner also argues that the specification teaches the elicitation of host immune response induced by a complex comprising CA 125 and the B43.13 murine monoclonal antibody (mAb) or antigen-binding fragment thereof, but this data allegedly "does not provide any guidance for the selection of a different antibody which binds to CA 125, nor of antibodies which bind to epitopes of CA 125 that differ from the epitope bound by Mab 43.13." Applicants note, however, that the Examiner has acknowledged that the specification is enabling with respect to other anti-CA 125 antibodies binding the same epitope as that of B43.13 (*see*, for example, the paragraph bridging pages 2 and 3 of the August 8, 2006 Office Action). Thus new Claim 133 has been added accordingly.

To support her position, the Examiner cites a passage from WO 99/65517 (filed on June 15, 1999) as "post-filing date art," and asserts that:

> "...the post filing reference teaches the importance of targeting an epitope which is not a dominant epitope in order to elicit antibodies and immune recognition against subdominant epitopes and that not all murine antibodies will possess the criteria of targeting an epitope which is not a dominant human epitope. Without this information published in 1997 [sic], it would be undue experimentation in order to screen all possible antibodies, including antibodies from a multitude of experimental hosts and human antibodies, for the ability to evoke antibodies to a different epitope on CA 125 than that bound by the antibody or T-cell recognition of CA 125."

Applicants note that this passage is not a teaching from a "post-filing date art" – in fact, the exact same passage can be found on page 16, the last paragraph of the instant specification.

Applicants respectfully submit that the Examiner has misunderstood the disclosure of the instant specification and that of the priority documents.

The Teaching of the Instant Specification

The instant specification teaches that contacting a multi-epitopic antigen with a binding agent (such as an antibody or binding-fragment thereof) promotes the formation of a complex, the administration of which leads to *increased immunogenicity* of the host multi-epitopic antigen, and the elicitation of a humoral and/or cellular response *in vivo* (*see*, for example, page 14, 2nd full paragraph). There is no requirement, however, that the binding agent (*e.g.*, antibody) must bind to a non-dominant epitope of the multi-epitopic antigen in order to increase its immunogenicity or to produce the desired humoral and/or cellular response *in vivo*.

Pursuant to MPEP 2138.05, "[an] inventor need not understand precisely why his invention works in order to achieve an actual reduction to practice." *See Parker v. Frilette*, 462 F.2d 544, 547 (CCPA 1972). Nevertheless, while not wishing to be bound by any particular theory, the instant specification does provide several potential mechanisms through which the observed stimulated host immune responses (humoral and/or cellular) may occur. *See*, for example, page 20, 4th full paragraph, and page 25, last paragraph to page 26, 1st full paragraph. Specifically, in terms of the humoral response that produces antibodies, at least two mechanisms may be responsible for the observed enhanced immune responses – the Ab3 pathway (anti-anti-idiotype pathway) or the Ab1c pathway (also known as the Ab3' pathway).

Merely to illustrate, suppose there is a host antigen A (*e.g.*, CA 125), which may comprise 10 epitopes, E1 – E10, with E1 being the most dominant epitope as "seen" by the host immune system, and E10 being the least dominant. Further suppose that there is a monoclonal antibody Mab (*e.g.*, B43.13), which binds the E3 epitope on antigen A. Because the binding by Mab may have increased the immunogenicity of the host antigen A, once the Mab / A complex is administered to the host, the host immune system may now recognize other epitopes on antigen A, such as E2, E5, E6, *etc.*, and generate *host* anti-A antibodies (**the Ab1c / Ab3' pathway antibodies**) against such subdominant epitopes.

Alternatively or in addition, at least when the antibody Mab is from a heterologous species, such as when the host is a human and the Mab is a mouse monoclonal antibody, the host (human) immune system may recognize the mouse antibody Mab as foreign. Thus *host* anti-

idiotype antibodies Ab2β may be generated. Such Ab2β antibodies in turn trigger the production of *host* anti-anti-idiotype antibodies Ab3 (**the Ab3 pathway antibodies**), which also recognize E3 – the antigen A epitope bound by Mab.

Either way, an effective *host* antibody (humoral) response is triggered *in vivo* by injecting the Mab / A complex. Similarly, a cellular response is also produced in the host. *See* page 26, 2nd full paragraph.

No Undue Experimentation is Necessary

According to the teaching of the instant specification, binding of an antibody, for example, a heterologous antibody (*e.g.*, a murine antibody, such as B43.13), to a host antigen previously unable to elicit an effective host immune response (*e.g.*, a human antigen, such as CA 125) alters / enhances the host immune response against the antigen. As explained herein, there is no requirement for the antibody in the administered antibody-antigen complex to recognize a non-dominant epitope on the antigen, as the Examiner suggests. Also, there is no need to perform undue experimentation in order to screen for an antibody which, when complexed with CA 125, would trigger the effective host immune response.

Again, merely for the purpose of illustration, the above-referenced antigen A / antibody Mab example may also be used to make the point.

As a skilled artisan will understand, potential immune response against self-antigens (antigen A, *e.g.*, CA 125) is eliminated or suppressed during fetal development, by deletion of T- / B-cells capable of recognizing self-antigens. Thus in humans, for example, T- / B-cells capable of recognizing the most dominant antigen A epitope (E1) may not exist. However, T- / B-cells capable of recognizing the other subdominant A epitopes, such as E2-E10, may exist (but are suppressed). As a result, a host may not be able to mount an effective immune response (humoral or cellular) against cancer cells bearing antigen A. This is consistent with the Madiyalakan teaching in WO 99/65517 that it may be important to stimulate T-cell response against the subdominant self-epitopes (such as E2-E10) to eliminate cancer cells.

However, this disclosure does not mean that one must first select a specific subdominant epitope (such as E3, which in this hypothetical example is recognized by antibody Mab) in order

to produce an antibody that can elicit the desired host immune response. Rather, in view of the teaching of the instant specification, a skilled artisan can readily envision that other complexes, (*e.g.*, those comprising antibodies binding to epitopes E1, E2, E4, ..., or E10 of antigen A), can also be administered *in vivo*.

In the hypothetical example above, antibody Mab happens to bind E3, which is not the most dominant antigen A epitope as the host immune system "sees" and responds to the antigen. As a result, the A / Mab *complex* becomes more immunogenic compared to antigen A alone as an antigen. Without wishing to be bound by any particular theory, this may be because: (1) the complex is more efficiently taken up by the professional APC (Antigen Presenting Cells), (2) the antibody Mab is acting like an immune-stimulating adjuvant, (3) "[e]pitopes of the antigen are blocked by the complexing antibody and are either protected from processing or processed at different sequences, thus creating new peptides for MHC-binding," and/or (4) new antigen A epitopes are exposed due to conformational changes induced by Mab binding (*see* the paragraph bridging pages 40 and 41 of the instant specification). It is also possible that the antibody (*e.g.*, Mab) targets the complex to the Fc receptors on dendritic cells for more efficient processing.

As a result, host antibodies against antigen A may be produced through either the Ab3 pathway or the Ab1c pathway, or both. Like Mab, the Ab3 pathway host antibodies also recognize E3. In contrast, the Ab1c pathway antibodies may recognize E2 or any of E4-E10. Anti-E1 antibodies may not be present, because host B-cells against E1 are likely deleted during fetal development.

Similarly, a cellular immune response against antigen A-bearing cells may also be elicited.

Moreover, there is no requirement that Mab must bind to a subdominant epitope (such as E3 in this example). There is no obvious reason why the claimed methods will be non-functional if Mab happens to recognize E1, the most dominant antigen A epitope. Specifically, if Mab is produced in a mouse against a *human* (foreign) antigen A, there is no clonal deletion of mouse B-cells immunoreactive with the most dominant *human* A epitope E1. Thus Mab could well bind the most dominant antigen A epitope E1. When the A / Mab complex is injected into a

host, host Ab1c antibodies and/or Ab3 antibodies may be generated, with the host Ab1c antibodies recognizing (some or all of) E2-E10 of antigen A, and the host Ab3 antibodies recognizing E1 of antigen A. Even if no Ab3 antibodies are produced, the host Ab1c antibodies are still sufficient to provide an effective host anti-antigen A immune response.

Either way, a skilled artisan need not perform undue experimentation "to screen all possible antibodies, including antibodies from a multitude of experimental hosts and human antibodies," as the Office Action suggests, in order to identify other antibodies capable of resulting in elicitation of effective host immune response. A skilled artisan can readily carry out at most routine experimentation to produce new antigen-specific antibodies, or simply use existing antigen-specific antibodies in the subject methods. A skilled artisan can also carry out at most routine experimentation, such as using art-recognized functional assays, to verify that the identified antigen-specific antibodies are capable of forming complexes with the soluble tumor-associated antigen, and/or eliciting the desired humoral or cellular immune responses when the complex is administered to a host. A skilled artisan would appreciate that screening for such complexes and functions, if necessary, involves no more than routine experimentation, certainly no more than the amount of routine experimentation required to screen a hybridoma library for hybridoma clones producing a desired monoclonal antibody.

Experimental Support in the Specification

The Examiner asserts that "[t]he specification specifically demonstrates the success of the claimed method only with Mab 43.13. The specification does not provide any guidance for the selection of CA 125 that differ from the epitope bound by Mab 43.13." Applicants respectfully disagree.

The instant application discloses multiple working examples. For example, Figure 6 of the instant application explicitly discloses that two *different* anti-CA 125 antibodies, *i.e.*, B43.13 and B27.1, each recognizing a *different CA 125 epitope* (*see* page 40, line 17 of the specification), can both form an antibody / CA 125 complex that stimulates immune response (*see* Figure 6 legend on page 18). In contrast, as a negative control, an isotype-matched control antibody MOPC-21 was ineffective (Figure 6).

Since antibody B27.1 recognizes a CA 125 epitope distinct from that recognized by antibody B43.13, the data in the specification demonstrates that at least the two tested, different CA 125 / antibody complexes can both induce the desired immune responses.

Furthermore, Applicants submit herewith a Rule 132 Declaration (with **Exhibit A**) by inventor Birgit C. Schultes, Ph.D., which Declaration provides additional data showing that a third monoclonal antibody – AR9.6 – which recognizes yet another CA 125 epitope distinct from that recognized by B43.13, also strongly stimulates T-cell responses against CA 125 when dendritic cells present the AR9.6 – CA 125 complex to naive T-cells.

According to the Declaration, two different CA 125 complexes with two different anti-CA 125 monoclonal antibodies (*i.e.*, B43.13 and AR9.6) were tested for their abilities to stimulate human T-cell activation, as measured by two independent T-cell activation assays, the Intracellular Cytokine (ICC) staining assay for IFN-γ, and the CTL assay on CA 125-bearing cancer cell line NIH:OVCAR-3. Specifically, human peripheral blood leukocytes (PBLs) were first purified from three HLA-matched healthy donors. From these purified PBLs, about 70-85% pure human monocytes and about 80-90% pure human T-cells were then separately generated by negative selection. The purified monocytes were then used to generate immature dendritic cells (immature DCs) by culturing the monocytes in GM-CSF and IL-4. The resulting immature DCs were loaded with two different antigen-antibody complexes, namely the B43.13 / CA 125 complex and the AR9.6 / CA 125 complex, and were further matured with TNF-α and IFN-α and used to stimulate the purified T-cells. As controls, immature DCs were also loaded with either CA 125 alone, B43.13 alone, AR9.6 alone, or medium (as a negative control), and these control loaded immature DCs were matured similarly, and used similarly for T-cell stimulation. The results clearly indicate that, in both the CTL assay and the ICC assay, both the B43.13 / CA 125 complex and the AR9.6 / CA 125 complex significantly stimulated T-cell activation compared to either antibody alone, antigen alone, or the negative control (media alone).

These experiments further demonstrate that no undue experimentation is necessary to practice the full scope of the claimed invention.

In summary, the instant specification itself has provided at least two working examples (including but not limited to complexes comprising the mouse monoclonal antibody B43.13) falling within the scope of the claims to show that antibodies or antigen-binding fragments thereof alter or enhance the host immune response against CA 125. Further experiments in the Rule 132 Declaration submitted herewith provide additional working examples using yet another anti-CA 125 monoclonal antibody AR9.6. Thus, all pending claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

Double Patenting Rejections

Claims 30, 71, 76, 98, 99, 103-110, 113, 114, 117-119, and 123-128 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 30, 71, 76, 98, 99, 103-110, 113, 114, 117-119, and 123-128 of U.S. Patent 6,241,985.

Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, as appropriate, upon indication of allowable subject matter.

Claims 30, 71, 76, 98, 99, 103-110, 113, 114, 117-119, and 123-128 are also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 276-282, 293-302, 313-322, and 333-338 of co-pending Application No. 09/376,604.

Applicants submit that, pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

If the allegedly conflicting claims are first allowed in the co-pending U.S. Application 09/376,604 and appear in an issued U.S. patent, Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, as appropriate, upon indication of allowable subject matter.

Claim Objection

Claim 88 is maintained as objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants submit that Claim 88 depends on allowable claims (*see* argument above). Nevertheless, Applicants have amended Claim 88 to become an independent claim incorporating all limitations of the claims from which it previously depended. Therefore, amended Claim 88 is allowable. Reconsideration and withdrawal of the objection are respectfully requested.

CONCLUSION

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **AREX-P02-004**.

Dated: February 8, 2007

Respectfully submitted,

By_____

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